

MODELLER

**“Protein Structure and Function Analysis”
SS2010**

Benjamin Wellmann

- Motivation
- MODELLER
 - Alignment
 - Spatial Restraints
 - Limitations
- Accuracy Evaluation

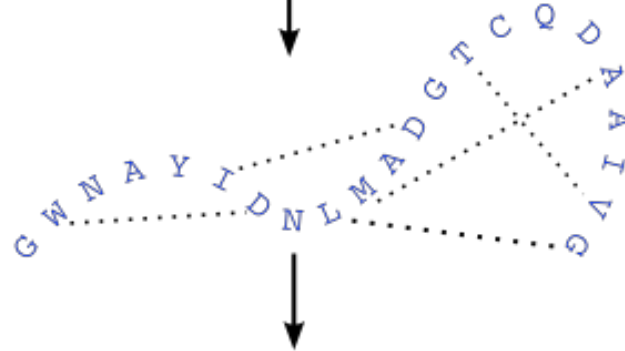
- Sequence \longleftrightarrow Structure gap
 - 10 million sequences in UniProt
 - 65000 in PDB
- Similar sequence \rightarrow similar structure
 - Use existing 3D structures
 - Comparative modeling

1. Align sequence with structures

Template structure(s)
Target sequence

SWQTYVDTNLVGTGAVTQA - - AI
- GWNAYIDNLMADGTCQDAAIVG

2. Extract spatial restraints

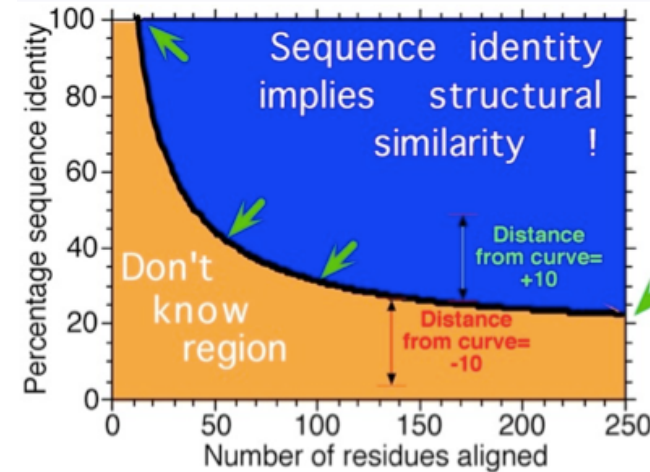


3. Satisfy spatial restraints



Sali & Blundell, 1993

- Search for sequence similar structures
 - Blast, ClustalW etc.
 - Sequence identity > 40 %
- Align target with template(s)
 - Inspect them carefully



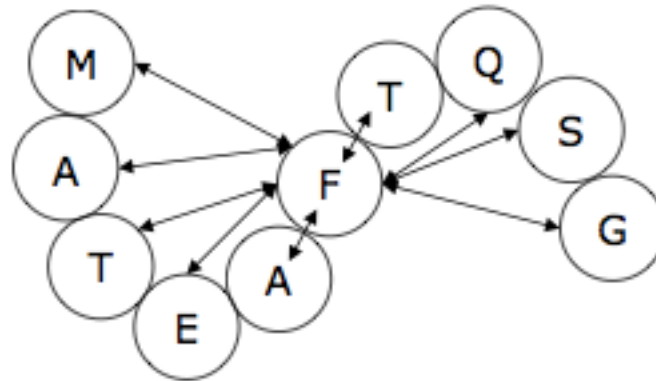
Rost, Lecture PP, 2010

Seq: HSLTRYFVRFLYSITFISLFPRAD
Tem: HFLTK-FMVALYSLIFISTFARAK
Tem: CSNTRYSVNFLY--NTMLFPAAD

- Generate restraints from alignment
- Geometrical criteria
 - transformed to prob. density function
 - Based on 105 family alignments (Šali & Overington, '94)
- Recent expansion uses electron density maps from cryo-EM
 - refine low-res results

- 31 spatial restrains
 - 8 Energy related (CHARMM 22)
 - 19 Geometry related
 - 4 Experimental / special

Text

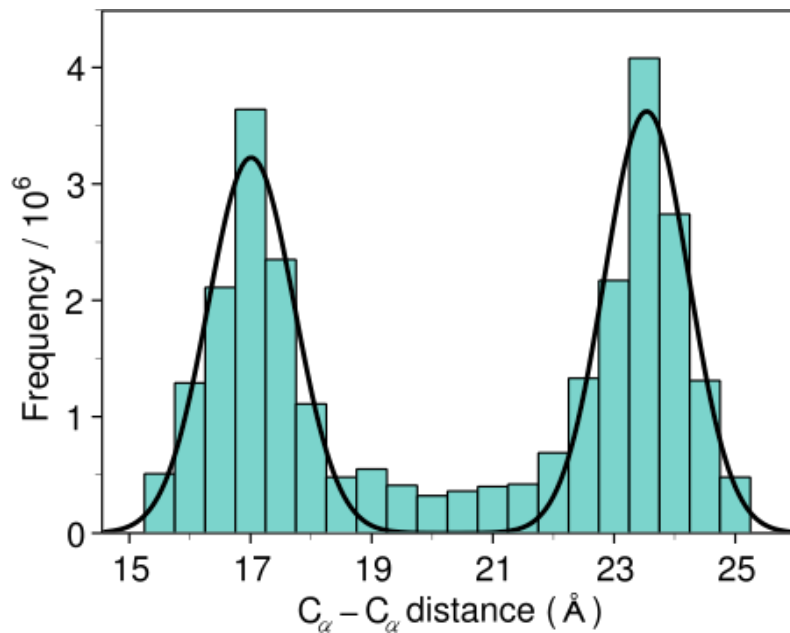


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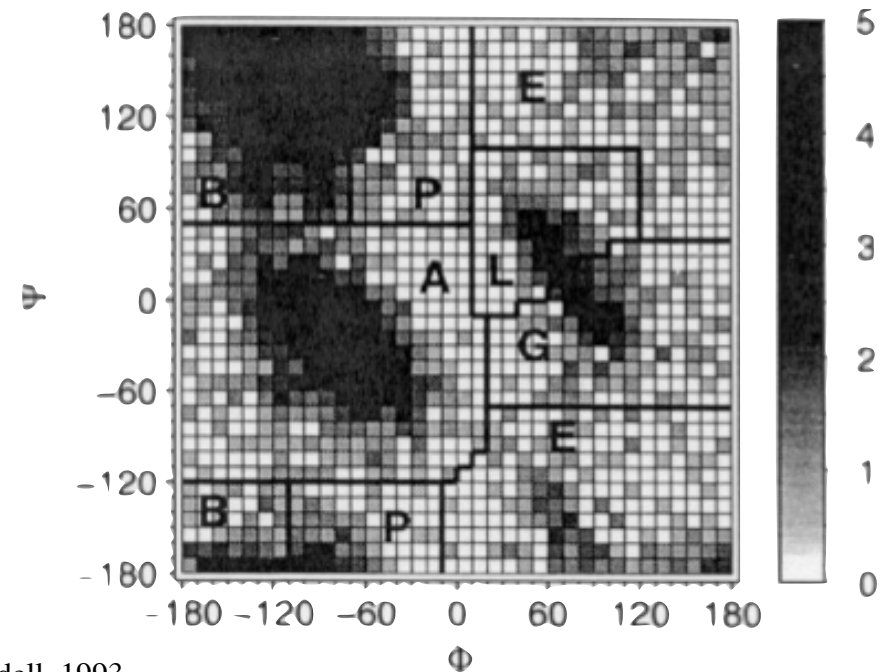
Table 1:
Restrained Physical Quantity

1	Bond length potential
2	Bond angle potential
3	Stereochemical cosine dihedral potential
4	Stereochemical improper dihedral potential
5	soft-sphere overlap restraints
6	Lennard-Jones 6-12 potential
7	Coulomb point-point electrostatic potential
8	H-bonding potential
9	Distance restraints 1 ($C_{\alpha}-C_{\alpha}$)
10	Distance restraints 2 (N-O)
11	Mainchain Φ dihedral restraints
12	Mainchain Ψ dihedral restraints
13	Mainchain Ω dihedral restraints
14	Sidechain χ_1 dihedral restraints
15	Sidechain χ_2 dihedral restraints
16	Sidechain χ_3 dihedral restraints
17	Sidechain χ_4 dihedral restraints
18	Disulfide distance restraints
19	Disulfide angle restraints
20	Disulfide dihedral angle restraints
21	X lower bound distance restraints
22	X upper bound distance restraints
23	Distance restraints 3 (SDCH-MNCH)
24	Sidechain χ_3 dihedral restraints
25	(Φ, Ψ) binomial dihedral restraints
26	Distance restraints 4 (SDCH-SDCH)
27	Distance restraints 5 (X-Y)
28	NMR distance restraints 6 (X-Y)
29	NMR distance restraints 7 (X-Y)
30	Minimal distance restraints
31	Non-bonded spline restraints

- Computation based on related proteins
 - extract averages, standard deviations

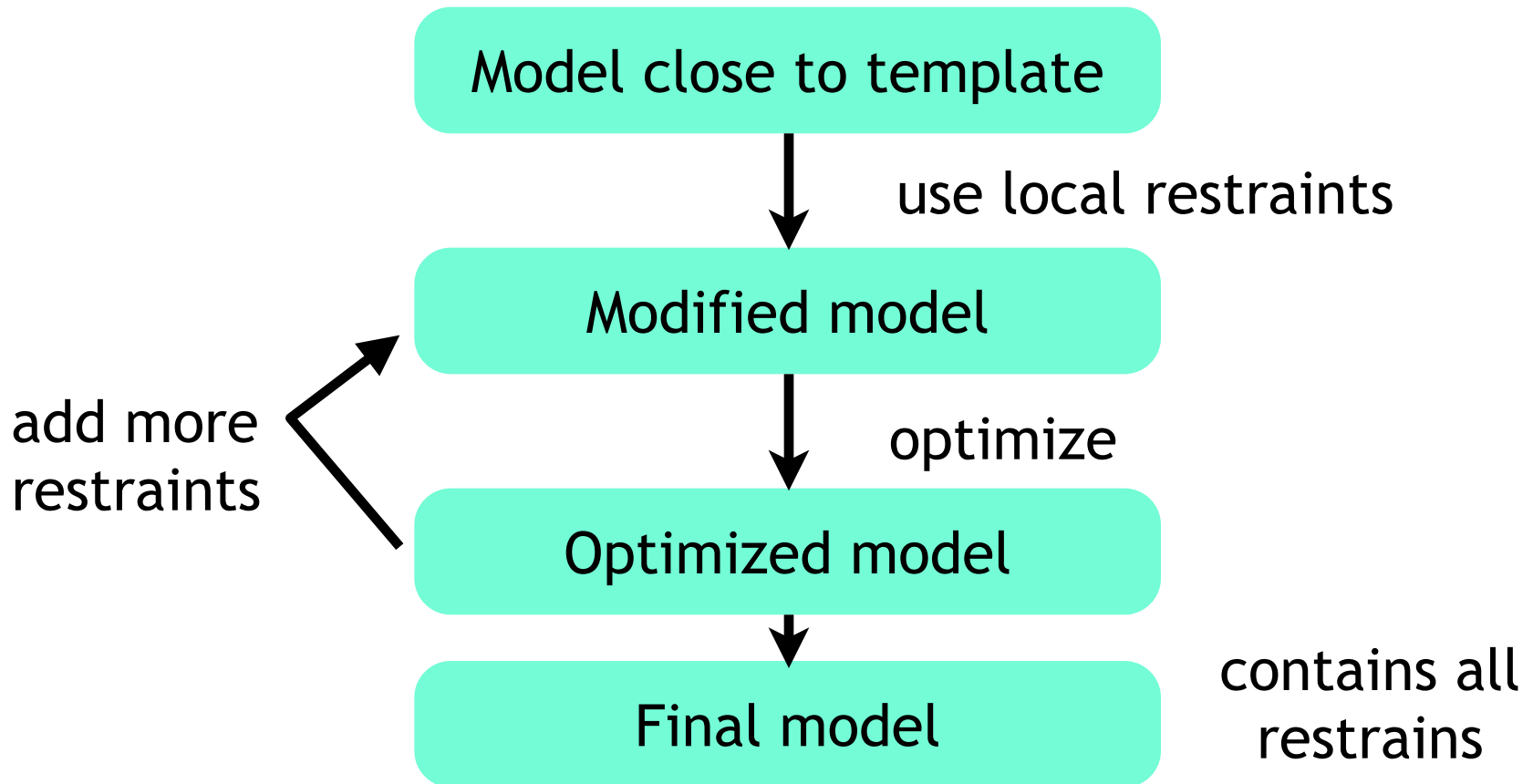


Sali & Blundell, 1993



Satisfy Spatial Restraints

- Find model with the highest probability
- Variable target function

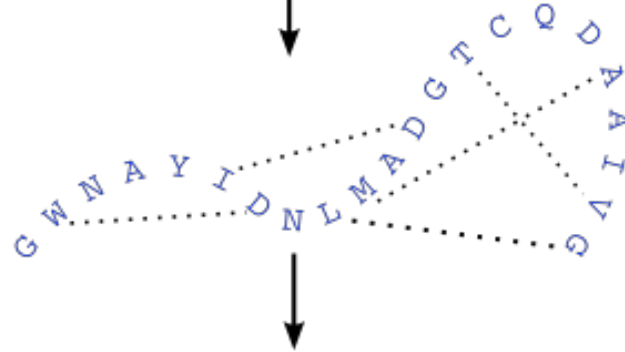


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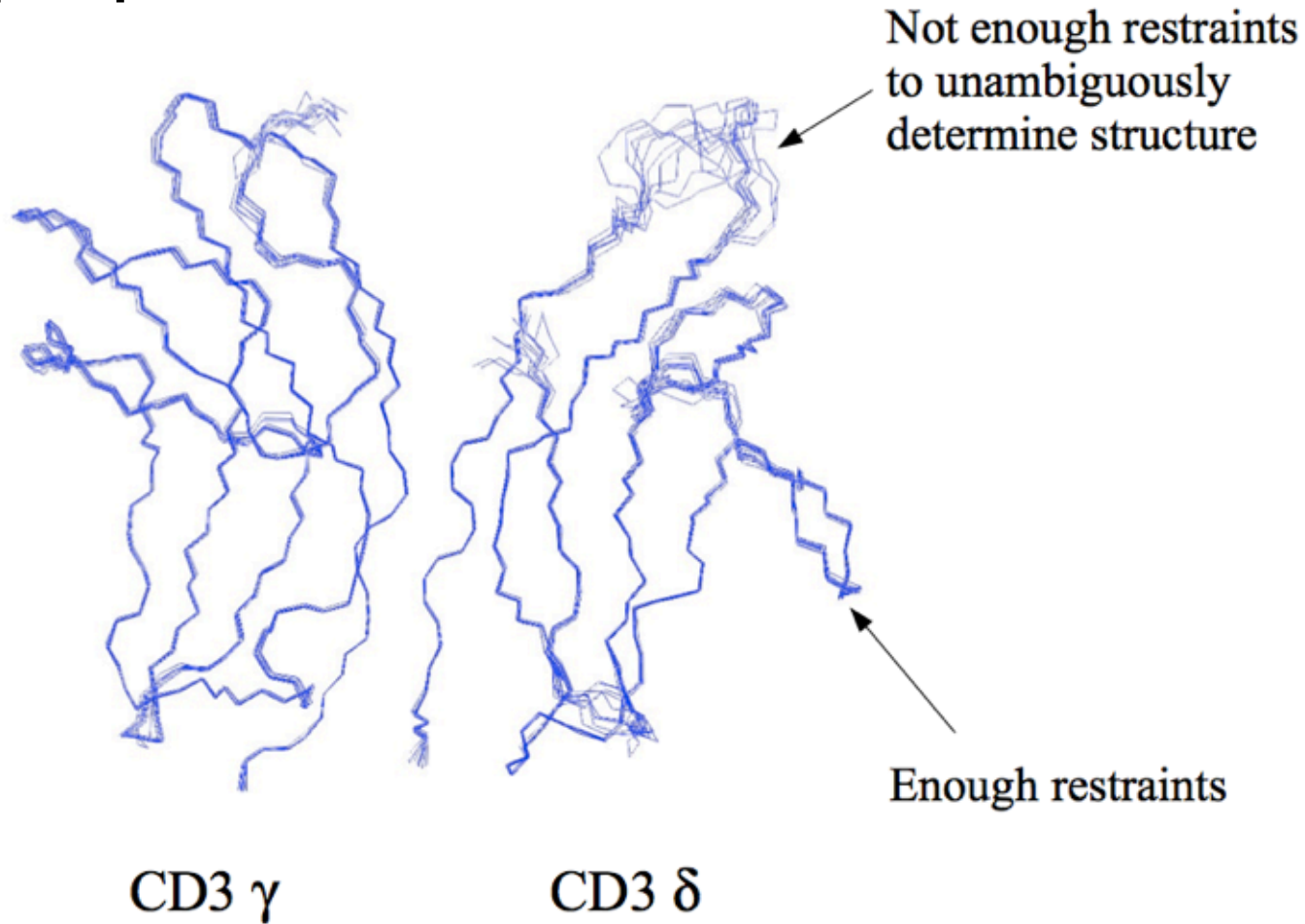


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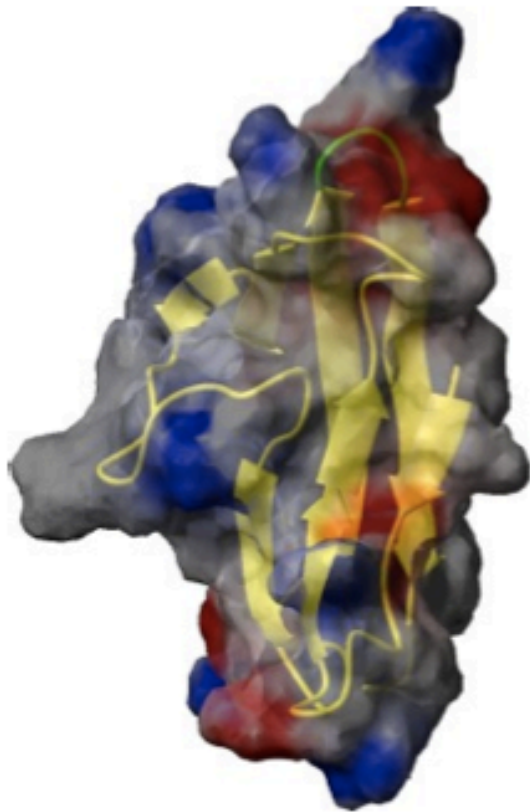


Sali & Blundell, 1993

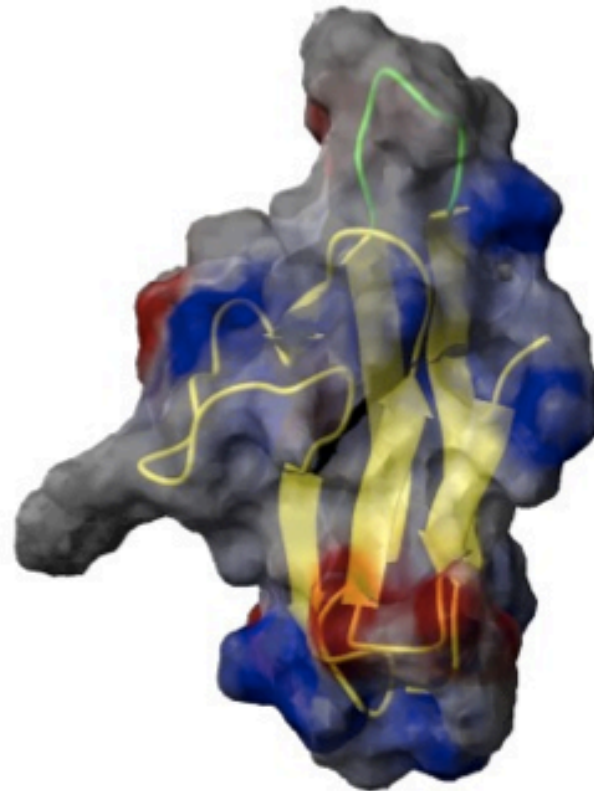
- Superpose of 10 models



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CD3 γ



CD3 δ

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PDB: 1JBj

- Scanning the PDB
 - similar anchors
 - similar loops
- Ab initio methods
 - simulated annealing
- Loop modeling is a major issue
 - Extremely flexible
 - Less conserved
 - Important for PPI

- CASP9
 - THE #1 contest
- EVA
 - Evaluation of Automatic protein structure prediction
 - last updated 2001



Thanks for your attention!

Questions?